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EXAMINER	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/576,047	HAMADA ET AL.	
	Examiner	Art Unit	
	KEVIN K. HILL	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 July 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2,5-9,11-19,24 and 25* is/are pending in the application.

4a) Of the above claim(s) *7-9,13,14 and 17-19* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2,5,6,11,12,15,16,24 and 25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

Election/Restrictions

Applicant has elected the following species without traverse, wherein:
i) the virus is adenovirus, as recited in claim 2;
ii) the carrier cell is A549, as recited in claims 4 and 21;
iii) the promoter is 1A1.3B, as recited in claim 5;
iv) the therapeutic compound is atelocollagen, as recited in claim 6 and 16;
v) the viral administration rate of the virus for immunological treatment is set between about 10^5 viral particles and 10^{11} viral particles for a patient with antibody negative to the virus, as recited in claim 12.

Because Applicant did not distinctly and specifically point out the supposed errors in the Group or species restriction requirement, the election has been treated as an election without traverse and the restriction and election requirement is deemed proper and therefore made final (MPEP § 818).

Amendments

Applicant's response and amendments, filed July 15, 2009, to the prior Office Action is acknowledged. Applicant has cancelled Claims 1, 3-4, 10 and 20-23, withdrawn Claims 7-9, 13-14 and 17-19, and amended Claims 24-25.

Claims 24-25 have been amended to recite the carrier cell to be either A549 cells or a mixture of A549 and 293 cells. In light of the species election requirement set forth in the Requirement for Restriction mailed May 29, 2007, whereupon Applicant elected the carrier cell species A549 in the response filed August 20, 2007, the mixture of A549 and 293 cells is withdrawn from further consideration as being drawn to a non-elected carrier cell species, there being no allowable generic or linking claim.

Claims 7-9, 13-14 and 17-19 are pending but withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a non-elected invention, there being no allowable generic or linking claim.

The Examiner acknowledges Applicant's request for rejoinder of Claims 7-9, 13-14 and 17-19. However, the present claims under examination are not yet in allowable form.

Claims 2, 5-6, 11-12, 15-16 and 24-25 are under consideration.

Priority

This application is a 371 of PCT/JP04/15220, filed October 15, 2003. A certified copy of PCT/JP04/15220, filed October 15, 2003, is filed with the instant application. Accordingly, the effective priority date of the instant application is granted as October 15, 2003.

Acknowledgment is made of Applicant's claim for foreign priority under 35 U.S.C. 119(a)-(d) of JP 2003-354983, filed October 15, 2003.

However, it is noted that, the application PCT/JP04/15220, filed October 15, 2003 is in Japanese. Therefore, without a certified translation of PCT/JP04/15220, filed October 15, 2003, the effective filing date for the instant claims is the filing date of the instant application, April 14, 2006.

Examiner's Note

Unless otherwise indicated, previous objections/rejections that have been rendered moot in view of the amendment will not be reiterated. The arguments in the July 15, 2009 response will be addressed to the extent that they apply to current rejection(s).

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Specification

1. **The disclosure is objected to because of the following informalities:**

The specification discloses that Figures 25a and 25b illustrate the effects of A549 carrier cells versus a mixture of A549 and 293 carrier cells ([0125], Specification filed April 14, 2006; pg 35, Specification filed February 18, 2008). However, the Figure 25 legends annotate only the 1x, 2x or 3x injection of the adenovirus and the figures do not illustrate the differences between the two carrier cell populations.

Appropriate correction and/or clarification is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. **Claims 11-12, 15-16 and 25 are rejected under 35 U.S.C. 112, second paragraph**, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 25 recites a first carrier cell (part (a)) and a second carrier cell (part (c)). The claim is indefinite because it is unclear if the A549 carrier cell population of part (d) refers to the carrier cell of part (a) or of part (c). To put it another way, it is unclear if the carrier cell population of part (a) is the same cells as the carrier cell population of part (c).

The working examples in the specification fail to disclose the administration of a carrier cell population prior to the administration of a non-proliferative virus for immunological treatment whereby said carrier cell population of step (a) is the same as the step (c) carrier cell population infected with the oncolytic virus.

Dependent claims are included in the basis of the rejection because although they recite and encompass the carrier cells, they do not clarify which carrier cells are required to comprise A549 cells.

Appropriate correction and/or clarification is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

New matter

3. **Claims 2, 5-6, 11-12, 15-16 and 24-25 are rejected under 35 U.S.C. 112 first paragraph**, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention because the specification as originally filed does not describe the invention as now claimed. Claims 24 and 25 have been amended to recite the carrier cell administered before the non-proliferative virus for immunological treatment is the same as the carrier cell infected with the oncolytic virus, wherein said carrier cell is an A549 cell. Clear support for the amendment cannot be found in the instant application or priority documents. Accordingly, the amendment(s) to Claims 24 and 25 is considered to constitute new matter.

> MPEP 2163.06 notes "IF NEW MATTER IS ADDED TO THE CLAIMS, THE EXAMINER SHOULD REJECT THE CLAIMS UNDER 35 U.S.C. 112, FIRST PARAGRAPH - WRITTEN DESCRIPTION REQUIREMENT. *IN RE RASMUSSEN*, 650 F.2D 1212, 211 USPQ 323 (CCPA 1981)." MPEP 2163.02 teaches that "WHENEVER THE ISSUE ARISES, THE FUNDAMENTAL FACTUAL INQUIRY IS WHETHER A CLAIM DEFINES AN INVENTION THAT IS CLEARLY CONVEYED TO THOSE SKILLED IN THE ART AT THE TIME THE APPLICATION WAS FILED...IF A CLAIM IS AMENDED TO INCLUDE SUBJECT MATTER, LIMITATIONS, OR TERMINOLOGY NOT PRESENT IN THE APPLICATION AS FILED, INVOLVING A DEPARTURE FROM, ADDITION TO, OR DELETION FROM THE DISCLOSURE OF THE APPLICATION AS FILED, THE EXAMINER SHOULD CONCLUDE THAT THE CLAIMED SUBJECT MATTER IS NOT DESCRIBED IN THAT APPLICATION". MPEP 2163.06 further notes "When an amendment is filed in reply to an objection or rejection based on 35 U.S.C. 112, first paragraph, a study of the entire application is often necessary to determine whether or not "new matter" is involved. *Applicant should therefore specifically point out the support for any amendments made to the disclosure*" (emphasis added).

In the instant case, while the specification discloses the use of a carrier cell population to be administered to a subject before the virus for immunological treatment and a carrier cell population infected with an oncolytic virus to be administered to the subject after waiting for a period of time, the specification discloses no example whereby a first carrier cell population for tumor vaccination is administered to the patient before administering the virus for immunological treatment is an A549 cell. The specification also fails to disclose an example whereby the first carrier cell population for tumor vaccination is administered to the patient before administering the virus for immunological treatment is the same as the second population of carrier cells infected with the oncolytic virus. While OVHM cells were used for tumor vaccination (Figures 22 and 32), said cells are different from the A549 carrier cells infected with adenovirus. Similarly, while A549 cells infected with adenovirus were used for tumor/viral vaccination prior to tumor formation (Figures 23-24), such examples did not perform the vaccination step with an un-infected carrier cell prior to the vaccination step with a non-

proliferative virus, nor subsequent administration of a carrier cell infected with an oncolytic virus.

Thus, the amendment is a departure from or an addition to the disclosure of the application as filed.

Alternatively, if Applicant believes that support for the first carrier cell population for tumor vaccination administered to the patient before administering the virus for immunological treatment is the same as the second population of carrier cells infected with the oncolytic virus, is present and clearly envisaged in the instant application or earlier filed priority documents, applicant must, in responding to this Office Action, point out with particularity, where such support may be found.

Applicant did not indicate where the limitations are supported by the original specification, or how, as is Applicant's burden. See MPEP §714.02, last sentence of the third paragraph from the end and MPEP §2163.06 (I) last sentence.

Claim Rejections - 35 USC § 103

4. **The prior rejection of Claims 11-12 and 25 under 35 U.S.C. 103(a)** as being unpatentable over Lambright et al (Ann. Thorac. Surg. 68:1756-1762, 1999; *of record in IDS) in view of Morrison et al (J. Virol. 68(2):689-696, 1994) and Kirn et al (Nature Medicine 7(7):781-787, 2001) **is withdrawn** in light of Applicant's amendment to the claims.

5. **The prior rejection of Claim 15 under 35 U.S.C. 103(a)** as being unpatentable over Lambright et al (Ann. Thorac. Surg. 68:1756-1762, 1999; *of record in IDS) in view of Morrison et al (J. Virol. 68(2):689-696, 1994) and Kirn et al (Nature Medicine 7(7):781-787, 2001), as applied to Claims 11-12 and 25 above, and in further view of Terman (2002/0177551 A1; *of record) **is withdrawn** in light of Applicant's amendment to the claims.

6. **The prior rejection of Claim 16 under 35 U.S.C. 103(a)** as being unpatentable over Lambright et al (Ann. Thorac. Surg. 68:1756-1762, 1999; *of record in IDS) in view of Morrison et al (J. Virol. 68(2):689-696, 1994) and Kirn et al (Nature Medicine 7(7):781-787, 2001), as

applied to Claims 11-12 and 25 above, and in further view of Ochiya et al (Curr. Gene Therapy 1: 31-52, 2001; *of record) **is withdrawn** in light of Applicant's amendment to the claims.

7. **The prior rejection of Claims 2 and 24 under 35 U.S.C. 103(a)** as being unpatentable over Lambright et al (Ann. Thorac. Surg. 68:1756-1762, 1999; *of record in IDS) in view of Morrison et al (J. Virol. 68(2):689-696, 1994) and Kirn et al (Nature Medicine 7(7):781-787, 2001), as applied to Claims 11-12 and 25 above, and in further view of Molnar-Kimber et al (WO 99/45783; September 16, 1999;* of record in IDS) and Inglis et al (U.S. Patent 5,837,261) **is withdrawn** in light of Applicant's amendment to the claims.

8. **Claims 2, 11-12 and 24-25 are rejected under 35 U.S.C. 103(a)** as being unpatentable over Szalay et al (U.S. 2005/0031643; filed June 18, 2004; priority to June 18, 2003) in view of Molnar-Kimber et al (WO 99/45783; *of record in IDS) and Harrison et al (2001; *of record).

Applicant cannot rely upon the foreign priority papers to overcome this rejection because a translation of said papers has not been made of record in accordance with 37 CFR 1.55. See MPEP §201.15.

Determining the scope and contents of the prior art.

With respect to Claim 25, Szalay et al disclose a method of cancer gene therapy [0020, 0026], the method comprising administering a carrier cell to a subject, followed by the step of administering a virus for immunological treatment (e.g., Examples 7-8). Szalay et al disclose the microorganism [virus] for immunological treatment can be a replication-incompetent variant of [same type of virus as] the therapeutic microorganism [0275]. The immunization achieves a T-cell mediated response, i.e. strong cytotoxic T cell responses [0125, 0139-0155, 0266].

Szalay et al disclose the method comprises a step of waiting a period after administering the virus for immunological treatment before continuing with the method of cancer gene therapy which comprises administering a therapeutic microorganism [0030]. Szalay et al disclose the method comprises the single or multiple administrations of one or more microorganisms to the subject, the dosing and frequency of which is determined by monitoring the subject and the immune response and/or tumor growth or inhibition, whereby the time period between

administrations may be about one to five days, about one week, about ten days, about two weeks, or about a month [0283-0285].

Szalay et al disclose the method comprises combinations of at least two microorganisms for formulation of a medicament for elimination of the tumors, whereby the administration can be effected simultaneously, sequentially or intermittently. The plurality of microorganisms can be administered as a single composition or as two or more compositions, whereby the two or more comprises viruses and eukaryotic cells [0290-0294].

Szalay et al do not disclose the method to comprise administering the oncolytic virus infected carrier cell, at least one time, to the patient to make the oncolytic virus act on a tumor cell within the patient, and wherein the oncolytic virus is proliferative in the tumor cell.

However, at the time of the invention, Molnar-Kimber et al disclosed a cancer gene therapy method comprising the step of waiting a period after administering a first carrier cell population into a subject to grow a second carrier cell population with an oncolytic virus to produce an oncolytic virus infected carrier cell, and administering said oncolytic virus infected carrier cell at least one time to a the patient (pg 31, lines 12-20).

Neither Szalay et al nor Molnar-Kimer et al et al disclose the [infected] carrier cell to be an A549 cell. However, at the time of the invention, Harrison et al taught the use of A549 cells to produce oncolytic viruses in a method to treat tumors. Harrison teach that their *in vivo* results are an extension of their *in vitro* experiments regarding the ability of A549 carrier cells to support replication of an oncolytic virus (pg 1330, col. 1, ¶1).

With respect to Claim 24, Szalay et al disclose kits containing the immunological and therapeutic microorganisms [0027]. Similarly, Molnar-Kimber et al disclose the pharmaceutical agents may be provided in kit form (pg 22, line 25-pg 23, line 15).

With respect to Claim 2, Szalay et al disclose the virus may be a herpes virus or an adenovirus [0188, 0218]. Similarly, Molnar-Kimer et al disclose the oncolytic virus may be a herpes virus or an adenovirus (pg 7, lines 6-8).

With respect to Claim 12, Szalay et al disclose the dosage regimen can be determined by one skilled in the art according to known clinical factors, e.g. 10^5 to 10^9 virus particles [0281].

Ascertaining the differences between the prior art and the claims at issue, and Resolving the level of ordinary skill in the pertinent art.

People of the ordinary skill in the art will be highly educated individuals, possessing advanced degrees, including M.D.'s and Ph.D.'s. They will be medical doctors, scientists, or engineers. Thus, these people most likely will be knowledgeable and well-read in the relevant literature and have the practical experience in virology, oncology and immunology. Therefore, the level of ordinary skill in this art is high.

"A person of ordinary skill in the art is also a person of ordinary creativity, not an automaton." *KSR International Co. v. Teleflex Inc.*, 550 U.S. ___, ___, 82 USPQ2d 1385, 1397 (2007). "[I]n many cases a person of ordinary skill will be able to fit the teachings of multiple patents together like pieces of a puzzle." *Id.* Office personnel may also take into account "the inferences and creative steps that a person of ordinary skill in the art would employ." *Id.* at ___, 82 USPQ2d at 1396.

Considering objective evidence present in the application indicating obviousness or nonobviousness.

It would have been obvious to one of ordinary skill in the art to substitute a first microorganism combination population comprising an oncolytic virus and a eukaryotic cell as taught by Szalay et al with an oncolytic virus infected carrier cell population as taught by Molnar-Kimber et al with a reasonable expectation of success because the simple substitution of one known element for another would have yielded predictable results to one of ordinary skill in the art at the time of the invention. M.P.E.P. §2144.07 states "The selection of a known material based on its suitability for its intended use supported a *prima facie* obviousness determination in *Sinclair & Carroll Co. v. Interchemical Corp.*, 325 U.S. 327, 65 USPQ 297 (1945). When substituting equivalents known in the prior art for the same purpose, an express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. *In re Fout*, 675 F.2d 297, 213 USPQ 532 (CCPA 1982). M.P.E.P.

§2144.06. In the instant case, an artisan would be motivated to substitute a first microorganism combination population comprising an oncolytic virus and a eukaryotic cell with an oncolytic virus infected carrier cell population because Szalay et al disclose that virus for immunological treatment may be used in combination with a therapeutic eukaryotic cell and/or oncolytic virus, and Molnar-Kimber et al teach that the carrier cells may produce a greater amount (tens, hundreds or thousands of virus copies) of oncolytic virus than can be directly administered to the subject in a given volume of fluid, the carrier cell may enable the virus to elude the subject's immune system and increase the likelihood that the virus will reach and kill a tumor cell, if the carrier cell exhibits binding affinity for the tumor cell, then the carrier cell will increase localization of the virus to the tumor cell (pgs 8-9, joining ¶), and Molnar-Kimber et al successfully demonstrated the ability of an oncolytic virus infected carrier cell population to therapeutically treat a tumor in a subject.

It also would have been obvious to one of ordinary skill in the art to substitute a first carrier cell type as taught by Szalay et al and/or Molnar-Kimber et al with a second carrier cell type, i.e. A549 cells, as taught by Harrison et al with a reasonable expectation of success because the simple substitution of one known element for another would have yielded predictable results to one of ordinary skill in the art at the time of the invention. M.P.E.P. §2144.07 states "The selection of a known material based on its suitability for its intended use supported a *prima facie* obviousness determination in *Sinclair & Carroll Co. v. Interchemical Corp.*, 325 U.S. 327, 65 USPQ 297 (1945). When substituting equivalents known in the prior art for the same purpose, an express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. *In re Fout*, 675 F.2d 297, 213 USPQ 532 (CCPA 1982). M.P.E.P. §2144.06. In the instant case, the carrier cells are recognized in the art as carrier cells for oncolytic viruses, and thus each performs the same function for the same purpose. An artisan would be motivated to substitute a first carrier cell type with a second carrier cell type, i.e. A549 cells, because A549 are routinely used in the art, each carrier cell achieves a particular oncolytic virus burst size, and Harrison et al successfully demonstrated A549 carrier cells to support replication of an oncolytic virus. Thus, selection of the carrier cell type is but a design choice for the artisan that reflects the oncolytic virus to be used in the cancer gene therapy method.

The cited prior art meets the criteria set forth in both *Graham* and *KSR*, and the teachings of the cited prior art provide the requisite teachings and motivations with a clear, reasonable expectation of success. Thus, absent evidence to the contrary, the invention as a whole is *prima facie* obvious.

Response to Arguments

Applicant argues that the method as defined in amended claim 25 can achieve a distinctly strong antitumor effect (shown in Figures 18a and 18b). The strong synergetic effect achieved by using a specific carrier cell and a nonproliferative virus in combination is unpredictable and non-obvious to a skilled artisan.

Applicant's argument(s) has been fully considered, but is not persuasive.

As a first matter, the instant claims require the following steps:

step 1: administering to a subject a carrier cell,

step 2: administering a non-proliferative virus for immunological treatment

step 3: after waiting a period, administering a carrier cell infected with an oncolytic virus.

However, Applicant's pointed example was achieved by the following steps:

step 1: administering to a patient a virus for immunological treatment

step 2: implanting a first tumor cell type for tumor formation

step 3: injecting carrier cells infected with adenovirus into the tumor, whereby the carrier cells are a different cell type than the first tumor cell type.

Thus, Applicant's working example does not use the instantly claimed steps to achieve the synergistic effect, and thus not commensurate in scope to the claimed invention.

As a second matter, Applicant's working example is directed the use of an adenoviral vector and the administration of infected carrier cells at least six times directly to the tumor in order to achieve the antitumor effect. Applicant contemplates the oncolytic adenovirus is infected from the carrier cells to the target tumor cells by cell to cell interaction (pg 26, Specification). However, the instant claims broadly encompass any viral vector, the

administration of infected carrier cells anywhere in the patient's body, and require no more than a single administration of infected carrier cells.

The art recognizes that the efficacy of an oncolytic virus will depend on several factors: the number of virions produced by each infected cell, the duration of the replication cycle from infection to tumor cell lysis and release of infectious particles, the physical characteristics determining viral spread within a tumor, and the inherent antigenicity of the virus which will influence the timing and magnitude of the immune response (Kirn, pgs 520-522).

Thus, the method by which Applicant achieved the "strong synergistic effect by using a specific carrier cell and a nonproliferative virus in combination" is not commensurate in scope to the instant claims.

9. **Claim 15 is rejected under 35 U.S.C. 103(a)** as being unpatentable over Szalay et al (U.S. 2005/0031643; filed June 18, 2004; priority to June 18, 2003) in view of Molnar-Kimber et al (WO 99/45783; *of record in IDS) and Harrison et al (2001; *of record), as applied to Claims 2, 11-12 and 24-25 above, and in further view of Terman (2002/0177551 A1; *of record).

Determining the scope and contents of the prior art.

Neither Szalay et al, Molnar-Kimber et al nor Harrison et al disclose the method to comprise the step of administering the oncolytic virus infected carrier cell by intratumoral injection. However, at the time of the invention, Terman disclosed a method of treating tumors comprising a step of administering to a patient *in vivo* with 10^{10} virus particles (pg 159, [2067]) comprising a nucleic acid viral vector to induce a CTL reaction, and after a predetermined period of time, e.g., at least three weeks (pg 94, Table V), the method further comprising a step of administering to said patient carrier cells infected with an oncolytic virus (pg 54, [0544, 0549]; pg 90-91, [1057-1058, 1060, Example V]), wherein said carrier cell may be a tumor cell (pg 8, [0052]), wherein the carrier cell infected with an oncolytic virus is administered to the patient into the host tumor (pg 90, [1056]).

Ascertaining the differences between the prior art and the claims at issue, and Resolving the level of ordinary skill in the pertinent art.

People of the ordinary skill in the art will be highly educated individuals, possessing advanced degrees, including M.D.'s and Ph.D.'s. They will be medical doctors, scientists, or engineers. Thus, these people most likely will be knowledgeable and well-read in the relevant literature and have the practical experience in virology, oncology and immunology. Therefore, the level of ordinary skill in this art is high.

"A person of ordinary skill in the art is also a person of ordinary creativity, not an automaton." *KSR International Co. v. Teleflex Inc.*, 550 U.S. ___, ___, 82 USPQ2d 1385, 1397 (2007). "[I]n many cases a person of ordinary skill will be able to fit the teachings of multiple patents together like pieces of a puzzle." *Id.* Office personnel may also take into account "the inferences and creative steps that a person of ordinary skill in the art would employ." *Id.* at ___, 82 USPQ2d at 1396.

Considering objective evidence present in the application indicating obviousness or nonobviousness.

It would have been obvious to one of ordinary skill in the art to substitute a first administration means, e.g. intraperitoneally as taught by Szalay et al and/or Molnar-Kimber et al with a second administration means, e.g. intratumorally, as taught by Szalay et al [0279] and/or Terman et al [1056] with a reasonable expectation of success because the simple substitution of one known element for another would have yielded predictable results to one of ordinary skill in the art at the time of the invention. M.P.E.P. §2144.07 states "The selection of a known material based on its suitability for its intended use supported a *prima facie* obviousness determination in *Sinclair & Carroll Co. v. Interchemical Corp.*, 325 U.S. 327, 65 USPQ 297 (1945). When substituting equivalents known in the prior art for the same purpose, an express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. *In re Fout*, 675 F.2d 297, 213 USPQ 532 (CCPA 1982). M.P.E.P. §2144.06. In the instant case, the ordinary artisan recognizes that the oncolytic virus infected carrier cell may be placed into, adjacent to, near or far from the tumor for treatment, and thus there are but four design options immediately envisaged by the routineer. An artisan would be motivated to try administering the oncolytic virus infected carrier cell by intratumoral injection in a cancer gene therapy method because such direct placement of the oncolytic virus infected

carrier cell would allow the oncolytic virus to infect the tumor cells to be treated with minimal or no exposure to neutralizing antibodies, and thereby improve the likelihood of killing the undesired tumor cells (Molnar-Kimber et al, pgs 44-45).

The cited prior art meets the criteria set forth in both *Graham* and *KSR*, and the teachings of the cited prior art provide the requisite teachings and motivations with a clear, reasonable expectation of success. Thus, absent evidence to the contrary, the invention as a whole is *prima facie* obvious.

10. **Claims 6 and 16 rejected under 35 U.S.C. 103(a)** as being unpatentable over Szalay et al (U.S. 2005/0031643; filed June 18, 2004; priority to June 18, 2003) in view of Molnar-Kimber et al (WO 99/45783; *of record in IDS), Harrison et al (2001; *of record) and Terman (2002/0177551 A1; *of record), as applied to Claims 2, 11-12, 15 and 24-25 above, and in further view of Ochiya et al (2001; *of record).

Determining the scope and contents of the prior art.

Neither Szalay et al, Molnar-Kimber et al nor Harrison et al nor Terman et al disclose the method to comprise administering atellocollagen with the oncolytic virus infected carrier cells. However, at the time of the invention, Ochiya et al reviewed the advantages of using atelocollagen to mediate controlled-release of bioactive agents of molecular medicines (pg 33, Figure 1).

Ascertaining the differences between the prior art and the claims at issue, and Resolving the level of ordinary skill in the pertinent art.

People of the ordinary skill in the art will be highly educated individuals, possessing advanced degrees, including M.D.'s and Ph.D.'s. They will be medical doctors, scientists, or engineers. Thus, these people most likely will be knowledgeable and well-read in the relevant literature and have the practical experience in virology, oncology and immunology. Therefore, the level of ordinary skill in this art is high.

"A person of ordinary skill in the art is also a person of ordinary creativity, not an automaton." *KSR International Co. v. Teleflex Inc.*, 550 U.S. ___, ___, 82 USPQ2d 1385, 1397 (2007). "[I]n many cases a person of ordinary skill will be able to fit the teachings of multiple

patents together like pieces of a puzzle." *Id.* Office personnel may also take into account "the inferences and creative steps that a person of ordinary skill in the art would employ." *Id.* at ___, 82 USPQ2d at 1396.

Considering objective evidence present in the application indicating obviousness or nonobviousness.

It would have been obvious to one of ordinary skill in the art to combine atellocollagen with the oncolytic virus infected carrier cells with a reasonable expectation of success because all the claimed elements were known in the prior art and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combination would have yielded predictable results to one of ordinary skill in the art at the time of the invention. An artisan would be motivated to combine atellocollagen with the oncolytic virus infected carrier cells because Ochiya et al teach that atelocollagen may be designed to degrade *in vivo* or be surgically removed (pg 38, Figure 5), is useful for the prolonged release of viral vectors *in vivo* (pgs 40-41), and may be used as a carrier for cell-based therapies (pgs 46-47, Figure 12).

The cited prior art meets the criteria set forth in both *Graham* and *KSR*, and the teachings of the cited prior art provide the requisite teachings and motivations with a clear, reasonable expectation of success. Thus, absent evidence to the contrary, the invention as a whole is *prima facie* obvious.

11. **Claim 5 is rejected under 35 U.S.C. 103(a)** as being unpatentable over Szalay et al (U.S. 2005/0031643; filed June 18, 2004; priority to June 18, 2003) in view of Molnar-Kimber et al (WO 99/45783; *of record in IDS), Harrison et al (2001; *of record), Terman (2002/0177551 A1; *of record) and Ochiya et al (2001; *of record), as applied to Claims 2, 6, 11-12, 15-16 and 24-25 above, and in further view of Hamada et al (2003; *of record in IDS).

Determining the scope and contents of the prior art.

Neither Szalay et al, Molnar-Kimber et al nor Harrison et al nor Terman et al nor Ochiya et al disclose the oncolytic virus to comprise a 1A1.3B promoter. However, at the time of the

invention, Hamada et al taught the use of a tumor cell-activated 1A1.3B promoter in the context of an oncolytic virus for ovarian cancer gene therapy.

Ascertaining the differences between the prior art and the claims at issue, and Resolving the level of ordinary skill in the pertinent art.

People of the ordinary skill in the art will be highly educated individuals, possessing advanced degrees, including M.D.'s and Ph.D.'s. They will be medical doctors, scientists, or engineers. Thus, these people most likely will be knowledgeable and well-read in the relevant literature and have the practical experience in virology, oncology and immunology. Therefore, the level of ordinary skill in this art is high.

"A person of ordinary skill in the art is also a person of ordinary creativity, not an automaton." *KSR International Co. v. Teleflex Inc.*, 550 U.S. ___, ___, 82 USPQ2d 1385, 1397 (2007). "[I]n many cases a person of ordinary skill will be able to fit the teachings of multiple patents together like pieces of a puzzle." *Id.* Office personnel may also take into account "the inferences and creative steps that a person of ordinary skill in the art would employ." *Id.* at ___, 82 USPQ2d at 1396.

Considering objective evidence present in the application indicating obviousness or nonobviousness.

It would have been obvious to one of ordinary skill in the art to substitute a tumor cell-activated promoter as taught by Szalay et al and/or Molnar-Kimber et al for a 1A1.3B promoter as taught by Hamada et al in an oncolytic virus with a reasonable expectation of success because the simple substitution of one known element for another would have yielded predictable results to one of ordinary skill in the art at the time of the invention. M.P.E.P. §2144.07 states "The selection of a known material based on its suitability for its intended use supported a *prima facie* obviousness determination in *Sinclair & Carroll Co. v. Interchemical Corp.*, 325 U.S. 327, 65 USPQ 297 (1945). When substituting equivalents known in the prior art for the same purpose, an express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. *In re Fout*, 675 F.2d 297, 213 USPQ 532 (CCPA 1982). M.P.E.P. §2144.06. In the instant case, the prior art recognized that the use of a tumor

cell-activated promoter would confer or enhance specificity of viral replication in the tumor cells. The art also recognized the existence of many tumor-activated promoters, including 1A1.3B, wherein the 1A1.3B gene product is an art-recognized ovarian cancer marker antigen. Hamada et al successfully demonstrate ovarian cancer-specific 1A1.3B promoter activity and suggest the usefulness of the 1A1.3B promoter for the generation of ovarian cancer-specific oncolytic viral vectors for the development of cancer-specific oncolytic viral therapies.

The cited prior art meets the criteria set forth in both *Graham* and *KSR*, and the teachings of the cited prior art provide the requisite teachings and motivations with a clear, reasonable expectation of success. Thus, absent evidence to the contrary, the invention as a whole is *prima facie* obvious.

Conclusion

12. No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to KEVIN K. HILL whose telephone number is (571)272-8036. The Examiner can normally be reached on Monday through Friday, between 9:00am-6:00pm EST.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Joseph T. Woitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Kevin K. Hill/

Examiner, Art Unit 1633